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Excess female siblings and male fetal loss in families with systemic lupus erythematosus

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Abstract

Background—Systemic lupus erythematosus (SLE) occurs more frequently among woman than men. We undertook the present study to determine whether the male-female ratio in SLE families is different than expected by chance, and whether excess male fetal loss is found.

Methods—All SLE patients met the revised American College of Rheumatology Classification criteria, while SLE-unaffected subjects were shown not to satisfy these same criteria. Putative family relationships were confirmed by genetic testing. Pregnancy history was obtained from all subjects, including unrelated control woman. Adjusted Wald binomial confidence intervals (CI) were calculated for ratio of boys to girls in families and compared to the expected ratio of 1.06

Results—There were 2578 subjects with SLE with 6056 siblings. Considering all subjects, we found 3201 boys and 5434 girls (ratio=0.59, of 95% CI 0.576–0.602). When considering only the SLE-unaffected siblings, there were 2919 boys and 3137 girls (ratio=0.93, 95%CI 0.92–0.94). In both cases, the ratio of males-to-females is statistically different than the known birth rate. Among SLE patients as well as among their sisters and mothers there was an excess of male fetal loss compared to the controls.

Conclusion—Siblings of SLE patients are more likely to be girls than expected. This finding may be in part explained by excess male fetal loss, which is found among SLE patients and their first degree relatives.

Keywords

Systemic lupus erythematosus; sex ratio; fetal loss; pregnancy

Introduction

Systemic lupus erythematosus (SLE) is a chronic, inflammatory disease that can involve virtually any organ system. The disease is complex in its clinical manifestations and serology as well as genetics (1–3). However, patients have in common the finding of autoantibodies that typically bind nuclear components (2). SLE is more common and more severe in Americans with sub-Saharan African ancestry compared to white Americans (4).

Women are affected with SLE about 10 times more frequently than are men, notwithstanding the fact that men have more severe disease (reviewed in 5). The female predominance for the incidence of SLE holds for all age groups, though less extreme for pre-pubertal children and at older age beyond menopause in women (6). There are abnormalities in sex hormones among either women or men with SLE but when determined at the onset of illness prior to therapy one study has found no differences in estrogen or androgen serum levels (7). Another cross-sectional study of men with SLE found no difference in androgen levels when compared to men with other chronic illnesses without a sex-bias (8).

There are several theories for the female bias found in SLE, other than sex hormone differences. We have proposed that risk is related to the number of X chromosomes, not sex. This hypothesis is based on an increased risk of SLE in men with 47,XXY (Klinefelter's syndrome) and a lower risk of SLE among women with 45,XO (Turner's syndrome) (9,10) as well as an increase of 47,XXX among women with SLE (unpublished data). In a study of pediatric SLE patients and their families, Lehman and colleagues found fewer male siblings than expected, and proposed a genetic susceptibility factor that gives boys a risk of fetal demise and girls a risk of SLE (11). These two ideas are not mutual exclusive. The parsimonious explanation is a gene on X that is both over-expressed in individuals with two X chromosomes compared to one, and imparts a risk of SLE to girls as well as a risk of fetal death to boys.

We undertook the present study to determine whether there are excess female siblings in families with SLE, both adult and pediatric onset. In addition, we sought to determine whether male fetuses are found in excess among spontaneous abortions and stillbirths in families with SLE.

Methods

Lupus Family Registry and Repository. We have been collecting and storing clinical data, sera, plasma, DNA, peripheral blood mononuclear cells, and family structure for almost twenty years from families with SLE (12,13). Putative SLE patients complete an extensive questionnaire, are interviewed by medically trained personnel, and have medical records reviewed to ensure that the revised American College of Rheumatology SLE Classification Criteria are met (14,15). SLE unaffected family members complete the questionnaire and are interviewed if there is any indication that undiagnosed SLE might be present. All subjects have ANA, anti-dsDNA, anti-phospholipid, and anti-ENA determined in the Oklahoma Medical Research Foundation Clinical Immunology Laboratory.

Family Structure

Complete family structures are obtained for all patients and families. Relationships have been shown to be consistent with the represented relationships through genetic testing, originally with microsatellite markers, and now with single nucleotide polymorphism (SNP) typing.

Pregnancy History

History of pregnancy and its complications were recorded for all SLE patients as well as their female relatives. These data included total number of pregnancies, number of live born infants, spontaneous abortions, induced abortions, and stillbirths (defined as delivery of a non-viable infant beyond the first trimester of pregnancy). In addition, subjects were asked the sex of the conceptus for all pregnancies, including those that were not completed to term delivery.

Statistics

We compared categorical data using the chi square test. P values less than 0.05 were considered significant. Adjusted Wald binomial confidence intervals (CI) were calculated for ratio of boys to girls in families and compared to the expected ratio of 1.06, that is, 13 male births for every 12 female births (16).

Results

We studied 2578 subjects with SLE, who in total had 6056 siblings. When considering all individuals, there were 3201 boys and 5434 girls in the sibships of SLE patients (Table 1). Thus, the ratio of boys to girls was 0.59 (95% CI 0.576–0.602). The confidence intervals do not include the expected ratio of 1.06 boys to girls. Thus, there were significantly fewer boys in these SLE families than expected.

Of course, there is a possible statistical explanation. The boys-to-girls ratio in sibships with SLE patients may be skewed because of the SLE, which is 90% female. That is, because inclusion of the SLE probands biases the data, these individuals should be omitted from the analysis. Thus in order to correct for this potential bias, we excluded all subjects with SLE and examined the sibling sex ratio. In this case, there 6056 non-SLE-affected siblings of whom 2919 were boys and 3137 were girls (Table 1). Again, the ratio of 0.93 was less than expected and the 95% confidence intervals of 0.921 to 0.938 did not include the expected ratio of 1.06.

In addition to the previous study of pediatric SLE, another study also found a skewing of the sex ratio among the siblings of SLE patients (22). This study noted that the sex ratio was only biased toward girls in the pregnancy that produced the SLE patient and the subsequent pregnancy. We addressed this issue by examining the sex ratio in the pregnancy just before and just after the pregnancy that produced a child destined to develop SLE. This was performed in a random sample of 85 families from the LFRR in which all needed information was available, such as birth order, sex, and participation of all siblings. We found among children born immediately before the child who developed SLE there were 11 boys and 29 girls (0.39 ratio). In the pregnancy just after the one that produced a child that eventually had SLE, there were 19 boys and 34 girls (0.56 ratio). The sex ratio distortion before and after the lupus pregnancy, respectively, differed from expected ($OR_{\text{BEFORE}}=2.4$, $\chi^2=6.73$, $p<0.01$ and $OR_{\text{AFTER}}=1.93$, $\chi^2=5.54$, $p<0.05$). So, the sex bias was greater in the pregnancies prior to the birth of the child who would go on to acquire SLE, which stands in contrast to the previous report in which the sex bias for girls was found just after the ‘lupus’ pregnancy. Meanwhile, the difference we found between the pregnancy just before and just after the SLE birth was not statistically significant ($\chi^2=0.72$, $p=0.52$).

We also studied the sex distribution of fetal loss. Among the SLE patients, there 48 spontaneous abortions or stillbirths in which the sex was known. Of these, 15 were female and 31 were male infants (ratio=0.326, 95%CI=0.208–0.4710). In addition, among the mothers and sisters of SLE patients, we found 95 pregnancy losses in which the sex of the fetus was known. There were 31 females and 64 males fetuses among these (ratio 0.484,

95% CI=0.366–0.604). Among 1500 female controls, who were age-, sex-, and ethnicity-matched to the SLE patients, the ratio of male-to-female fetal loss was 0.95.

Discussion

SLE is found among women about ten times more often than among men. In fact, a female predominance is present for almost all diseases now considered autoimmune (17). Despite clear and known effects of sex hormones on the immune system, an explanation of autoimmune disease sexual dimorphism on the basis of sex hormones has not been elucidated (18), despite the appearance of new theories (19). Of course, there may not be a common mechanism across all autoimmune diseases. This is suggested by the fact that autoimmune thyroid disease (20) and type 1 diabetes mellitus (21) are associated with Turner's syndrome (female 45,XO), but this sex chromosome aneuploidy is probably not associated with SLE (9,10).

In a very large cohort of SLE patients, we find that there are fewer boys than expected among the siblings of the SLE patients. The ratio of boys to girls, both considering the subjects with SLE or excluding them, is very similar to that found in a small cohort of pediatric-onset SLE patients (11). In their study of 91 pediatric SLE patients, Moorthy and colleagues found a boy-to-girl ratio of about 0.6 with SLE patients included, and a ratio of 0.92 without SLE patients included. In the present study we find ratios of 0.59 and 0.93, with and without SLE patients considered, respectively. Of interest, Moorthy and colleagues did not find an abnormal male-to-female ratio among the siblings of patients with systemic onset juvenile idiopathic arthritis, a disease which does not have a sex bias (11). Only about 10% of our patients have pediatric onset of SLE. The effect we find when excluding the SLE probands is the statistically correct one, and is present in families with either adult or pediatric disease onset (not shown).

Another study also found that the families of SLE patients have more girls than expected. Oleinick studied 191 SLE patients and their families. There were 279 male siblings and 302 female siblings, giving a ratio of 0.923 (22). This value is, of course, strikingly similar to that we find as well as that found among pediatric onset SLE (10). However, the strongest bias in sex of siblings of SLE patients was found in the pregnancy just after the birth of the SLE patient with no sex bias found in the pregnancy preceding the SLE pregnancy. The author concluded that there was an environmental factor leading to male fetal demise and female SLE since the sex bias was not uniform across the siblings. However, we find among a much greater number of SLE patients and their families (2578 SLE subjects with SLE and 6056 siblings) that the sex bias occurs both before and after the birth of the sibling who went on to have SLE.

Neither of the previous studies of sex bias among the families of SLE patients has studied the sex of infants spontaneously aborted or stillborn. Many women in our cohort did not know the sex of fetuses aborted in the first trimester, so our data come from a proportion of pregnancies that were not carried to term. There is no reason to suspect that there is a bias such that the women in these SLE families are more likely to know the sex of aborted or stillborn males, however. In any case, we find that fetuses aborted or stillborn are twice as likely to be male. This was true for SLE patients as well as their sisters and mothers.

Previous data of a sex bias just proximal to the birth of the SLE-affected subject were interpreted to mean an environmental factor was present (22). We have produced two pieces of data that bear on this question. First, we find increased male fetal loss not only among SLE patients but also among their first degree relatives, mothers and sisters who are not likely to share a common environment while pregnant. Second, we do not find the sex bias

among SLE siblings is confined to the pregnancy just after the SLE pregnancy. Thus, our data do not indicate an environmental component occurring around the birth of the SLE patient.

The present data, along with our previous data that the number of X chromosomes is a risk factor for SLE, can be combined into a single genetic possibility. Approximately 20% of genes on the X chromosome are not inactivated by typical Lyonization, which is mediated by CpG methylation (23). Thus, one possibility is that there is a non-inactivated X chromosome gene that has increased expression depending upon the number of X chromosomes. Or, an X chromosome gene could give a risk fetal demise when found homozygous, as in 46,XY males. But, when found heterozygous, as in most 46,XX females and 46,XXY males, the gene imparts an increased risk of SLE. In fact there is an example of such a gene acting in this way in another disease. Incontinentia pigmenti, a skin pigmentation disorder with other associated abnormalities (24), is caused by mutation in the NEMO gene (also known as IP2), which is located at Xq28 (25). The gene product is I κ B β , one of the two subunits of the IKK kinase that mediates the NF- κ B signaling cascade (26). Inheritance of this gene by a male conceptus most commonly results in fetal death, while the disease is found in those with two X chromosomes only.

There are other possibilities. Wallace has proposed that a gene on the Y chromosome might increase risk of fetal demise in males and therefore lead to the sex bias of SLE (24). This does not explain an increased risk of SLE in 47, XXY men (9), or in 47,XXX women compared to 46,XX woman (Scofield and Harley, unpublished data). A gene on an autosomal chromosome could be expressed in the male fetuses only and predispose to spontaneous abortion or stillbirth, and then in post-natal life be expressed in such a way as to predispose to SLE. There are a number of factors that change the sex ratio of live births. These include, but are not limited, to pre-eclampsia, maternal fatty liver, maternal measles, maternal chronic hepatitis B, maternal glucose, maternal multiple sclerosis, maternal age, polycystic ovarian disease, breast cancer, paternal (both parents) hormones levels at the time of conception, race/ethnicity, and even rate of coitus (28). For most of these factors, we do not have any information in our cohort, but hepatitis B may account for much of the sex ratio differences in the world (29).

Autoantibodies are another intriguing possibility. The HY antigens are encoded on the Y chromosome; and, therefore are present only in male cells. Women develop these antibodies after an allogeneic bone marrow transplant in which the donor was male; and, some women develop antibodies directed against these antigens after pregnancy with a boy (29,30). The presence of anti-HY antibodies is associated secondary pregnancy loss (that is, after a viable birth) with male spontaneous abortions and an increased ratio of female-to-male live births (31). Antibodies directed against N-methyl-D-aspartate (anti-NMDAR) is also of interest. These antibodies occur spontaneously or as a paraneoplastic process, especially associated with teratoma. In addition, these antibodies are related to SLE. Immunization with a peptide mimotope of DNA results not only anti-DNA but also anti-NMDAR. Pertinent to the results presented herein, recent data demonstrate that female mice immunized in this way have more male offspring than expected because of the demise of female fetuses (32). The effect on female fetuses is mediated by a sexually dimorphic expression of NMDAR in the brain. These findings, while opposite in terms of the affected sex, show in principle that maternal antibodies may cross the placenta and affect the fetus in a sex-specific manner (32). Thus, autoantibodies can induce sexually specific lethal damage to the developing fetus. In human disease, two pregnancies complicated by anti-NMDAR encephalitis have been reported with delivery of normal infants. However, the sex of the infants was not given (33).

It is easy to suppose that SLE patients might be more likely to produce such antibodies than non-SLE affected women. Furthermore, the relatives of SLE patients are more likely to have autoantibodies than controls without a family history of SLE (34–36). Production of autoantibodies, although not likely directly pathogenic, is associated with recurrent fetal loss in the first trimester of pregnancy (37–40). Thus, it is possible that anti-HY antibodies in SLE patients and their relatives are responsible for the lower number of male siblings and the increase loss of male fetuses. Conversely, anti-phospholipid antibodies are commonly found in SLE patients and are associated with late term pregnancy loss but this loss does not show a sex bias (41).

Women with SLE definitely have lower rates of birth compared to healthy controls (42,43). A lower rate of male births may in part explain this difference. This effect could be genetic or environmental, such as autoantibodies. It remains to be determined which one or possibly more than one of the possible mechanisms are involved in the lower ratio of male to female siblings in SLE families and the increase in male fetal loss. Elucidating such mechanisms that are responsible for these findings may greatly advance knowledge of the X chromosome dose effect in SLE, the sex bias in SLE families, and why women, and occasionally some men, acquire SLE.

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References

1. Crow MK. Developments in the clinical understanding of lupus. *Arthritis Res Ther*. 2009; 11:245. 2009. [PubMed: 19849817]
2. Kurien BT, Scofield RH. Autoantibody determination in the diagnosis of systemic lupus erythematosus. *Scand J Immunol*. 2006; 64:227–235. [PubMed: 16918691]
3. Flesher DL, Sun X, Behrens TW, Graham RR, Criswell LA. Recent advances in the genetics of systemic lupus erythematosus. *Exp Rev Clin Immunol*. 2010; 6:461–479.
4. Danchenko N, Satia JA, Anthony MS. Epidemiology of systemic lupus erythematosus: a comparison of worldwide disease burden. *Lupus*. 2006; 15:308–318. [PubMed: 16761508]
5. Lu LJ, Wallace DJ, Ishimori ML, Scofield RH, Weisman MH. Review: Male systemic lupus erythematosus: a review of sex disparities in this disease. *Lupus*. 2010; 19:119–129. [PubMed: 19946032]
6. Ramsey-Goldman, R.; Manzi, S. *Women Health*. Academic Press; 2000. Systemic lupus erythematosus; p. 704
7. Soares PM, Borba EF, Bonfa E, Hallak J, Corrêa AL, Silva CA. Gonad evaluation in male systemic lupus erythematosus. *Arthritis Rheum*. 2007; 56:2352–2361. [PubMed: 17599762]
8. Mackworth-Young CG, Parke AL, Morley KD, Fotherby K, Hughes GR. Sex hormones in male patients with systemic lupus erythematosus: a comparison with other disease groups. *Eur J Rheumatol Inflam*. 1983; 6:228–232.
9. Scofield RH, Bruner GR, Namjou B, Kimberly RP, Ramsey-Goldman R, Petri M, Reveille JD, Alarcon GS, Vila LM, Reid J, Harris B, Li S, Kelly JA, Harley JB, Danchenko N, Satia JA, Anthony MS. Klinefelter's syndrome (47,XXY) in male systemic lupus erythematosus patients: support for the notion of a gene-dose effect from the X chromosome. *Arthritis Rheum*. 2008; 58:2511–2517. [PubMed: 18668569]
10. Cooney CM, Bruner GR, Aberle T, Namjou-Khales B, Myers LK, Feo L, Li S, D'Souza A, Ramirez A, Harley JB, Scofield RH. 46,X,del(X)(q13) Turner's syndrome women with systemic lupus erythematosus in a pedigree multiplex for SLE. *Genes Immunol*. 2009; 10:478–481.
11. Moorthy LN, Peterson MG, Onel KB, Lehman TJ. Do children with lupus have fewer male siblings? *Lupus*. 2008; 17:128–131. [PubMed: 18250136]

12. Moser KL, Neas BR, Salmon JE, Yu H, Gray-McGuire C, Asundi N, Bruner GR, Fox J, Kelly J, Henshall S, Bacino D, Dietz M, Hogue R, Koelsch G, Nightingale L, Shaver T, Abdou NI, Albert DA, Carson C, Petri M, Treadwell EL, James JA, Harley JB. Genome scan of human systemic lupus erythematosus: evidence for linkage on chromosome 1q in African-American pedigrees. *Proc Natl Acad Sci U S A*. 1998; 95:14869–14874.
13. Rasmussen A, Sevier S, Kelly J, Glenn S, Aberle T, Cooney CM, Grether A, Goodmon E, Ning J, Tesiram J, Morrissey J, Powe T, Drexel M, Daniel W, Namjou B, Ojwang JO, Nguyen KM, Cavett JW, Te JL, James JA, Scofield RH, Moser KL, Gilkeson GS, Kamen DL, Carson C, Ballesteros MdC, Punaro MG, Quintero-del-Rio AL, Karp DR, Wallace DJ, Weisman M, Merrill J, Rivera R, Petri MA, Albert DA, Espinoza LR, Utset TO, Shaver TS, Arthur E, Anaya JM, Bruner GR, Harley JB. The Lupus Family Registry and Repository. *Rheumatol*. 2011; 50:47–59.
14. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, Schaller JG, Talal N, Winchester RJ. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum*. 1982; 25:1271–1277. [PubMed: 7138600]
15. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum*. 1997; 40:1725. [PubMed: 9324032]
16. Hardy, ICW. Sex Ratios: Concept and Research Methods. Chapter 14: Human sex ratios: adaptations and mechanism, problems and prospects. Cambridge: Cambridge University Press; 2002. p. 288
17. Cooper GS, Stroehla BC. The epidemiology of autoimmune diseases. *Autoimmun Rev*. 2003; 2:119–125. [PubMed: 12848952]
18. McMurray RW, May W. Sex hormones and systemic lupus erythematosus: review and meta-analysis. *Arthritis Rheum*. 2003; 48:2100–2110. [PubMed: 12905462]
19. Sekigawa I, Fujishiro M, Yamaguchi A, Kawasaki M, Inui A, Nozawa K, Takasaki Y, Takamori K, Ogawa H. A new hypothesis of the possible mechanisms of gender differences in systemic lupus erythematosus. *Clin Exp Rheumatol*. 2010; 28:419–423. [PubMed: 20460035]
20. El-Mansoury M, Bryman I, Berntorp K, Hanson C, Wilhelmsen L, Landin-Wilhelmsen K. Hypothyroidism is common in turner syndrome: results of a five-year follow-up. *J Clin Endocrinol Metab*. 2005; 90:2131–2135. [PubMed: 15623818]
21. Mortensen KH, Cleemann L, Hjerrild BE, Nexø E, Locht H, Jeppesen EM, Gravholt CH. Increased prevalence of autoimmunity in Turner syndrome--influence of age. *Clin Exp Immunol*. 2009; 156:205–210. [PubMed: 19298606]
22. Oleinick A. Family studies in lupus erythematosus. 1. Prenatal factors. *Arthritis Rheum*. 1969; 12:10–16. [PubMed: 5765684]
23. Carrel L, Willard HF. X-inactivation profile reveals extensive variability in X-linked gene expression in females. *Nature*. 2005; 434:400–404. [PubMed: 15772666]
24. Ehrenreich M, Tarlow MM, Godlewska-Janusz E, Schwartz RA. Incontinentia pigmenti (Bloch-Sulzberger syndrome): a systemic disorder. *Cutis*. 2007; 79:355–362. [PubMed: 17569396]
25. The International Incontinentia Pigmenti Consortium. Genomic rearrangement in NEMO impairs NF-kappa-B activation and is a cause of incontinentia pigmenti. *Nature*. 2000; 405:466–472. [PubMed: 10839543]
26. Courtois G, Israel A. IKK regulation and human genetics. *Curr Top Microbiol Immunol*. 2011; 349:73–95. [PubMed: 20845108]
27. Wallace DJ. A reason for the rarity of male lupus. *Lupus*. 1998; 7:60. [PubMed: 9493153]
28. James WH. The variations of human sex ratio at birth during and after wars, and their potential explanations. *J Theoretical Biol*. 2009; 257:116–123.
29. Miklos DB, Kim HT, Zorn E, Hochberg EP, Guo L, Mattes-Ritz A, Viatte S, Soiffer RJ, Antin JH, Ritz J. Antibody response to DBY minor histocompatibility antigen is induced after allogeneic stem cell transplantation and in healthy female donors. *Blood*. 2004; 103:353–359. [PubMed: 14512314]
30. Wadia PP, Sahaf B, Miklos DB. Recombinant antigen microarrays for serum/plasma antibody detection. *Meth Molec Biol*. 2011; 723:81–104.

31. Nielsen HS, Wu F, Aghai Z, Steffensen R, van Halteren AG, Spierings E, Christiansen OB, Miklos D, Goulmy E. H-Y antibody titers are increased in unexplained secondary recurrent miscarriage patients and associated with low male : female ratio in subsequent live births. *Human Reproduc.* 2010; 25:2745–2752.
32. Wang L, Zhou D, Lee J, Niu H, Faust TW, Frattini S, Kowal C, Huerta PT, Volpe BT, Diamond B. Female mouse fetal loss mediated by maternal autoantibodies. *J Exp Med.* 2012; 209:1083–1089. [PubMed: 22565825]
33. Kumar MA, Jain A, Dechant VE, Saito T, Rafeal T, Aizawa H, Dysart KC, Katayama T, Ito Y, Araki N, Abe T, Balice-Gordon R, Dalmau J. Anti-N-methyl-D-aspartate receptor encephalitis during pregnancy. *Arch Neurol.* 2010; 67:884–887. [PubMed: 20625099]
34. Li QZ, Karp DR, Quan J, Branch VK, Zhou J, Lian Y, et al. Risk factors for ANA positivity in healthy persons. *Arthritis Res Ther.* 2011; 13:R38. [PubMed: 21366908]
35. Marin GG, Cardiel MH, Cornejo H, Viveros ME. Prevalence of antinuclear antibodies in 3 groups of healthy individuals: blood donors, hospital personnel, and relative of patients with autoimmune diseases. *J Clin Rheumatol.* 2009; 15:325–329. [PubMed: 20009966]
36. Aggarwal R, Namjou B, Li S, D'Souza A, Tsao BP, Bruner BF, James JA, Scofield RH. Male-only systemic lupus. *J Rheumatol.* 2010; 37:1480–1487. [PubMed: 20472921]
37. Ticconi C, Rotondi F, Veglia M, Pietropolli A, Bernardini S, Ria F, Caruso A, Di Simone N. Antinuclear autoantibodies in women with recurrent pregnancy loss. *Am J Reproduc Immunol.* 2010; 64:384–392.
38. Abbassi-Ghanavati M. Thyroid autoantibodies and pregnancy outcomes. *Clin Obstet Gynecol.* 2011; 54:499–505. [PubMed: 21857181]
39. Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Thyroid antibody positivity in the first trimester of pregnancy is associated with negative pregnancy outcomes. *J Clin Endocrinol Metab.* 2011; 96:E920–E924. [PubMed: 21411559]
40. Thangaratinam S, Tan A, Knox E, Kilby MD, Franklyn J, Coomarasamy A. Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence. *BMJ.* 2011; 342:d2616. [PubMed: 21558126]
41. Salmon JE, Giraldi G, Locjshin MD. The antiphospholipid syndrome as a disorder initiated by inflammation: implications for the therapy of pregnant patients. *Nat Clin Pract Rheumatol.* 2007; 3:140–147. [PubMed: 17334336]
42. Smyth A, Oliveira GHM, Lahu BD, Bailey KR, Norby SM, Garvoic VD. A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. *Clin J Am Soc Nephrol.* 2010; 5:2060–2068. [PubMed: 20688887]
43. Elblom-Kullberg S, Kautianien H, Alha P, Helve T, Leirisalo-Repo M, Julkunen H. Reproductive health in women with systemic lupus erythematosus compared to population controls. *Scand J Rheumatol.* 2009; 38:375–380. [PubMed: 19308803]

Table 1

The sibships of SLE patients have excess girls compared to boys with inclusion of all siblings including the SLE patient as well as with the SLE patients excluded. The 95% confidence intervals in neither case cross the expected ratio of 1.06.

	All Siblings excluded	SLE patients
Boys	3201	2919
Girls	5434	3137
Ratio	0.59 (95% CI=0.576–0.602)	0.93 (95% CI=0.921–0.938)